



C9orf72 gene

chromosome 9 open reading frame 72

Normal Function

The *C9orf72* gene provides instructions for making a protein that is found in various tissues. The protein is abundant in nerve cells (neurons) in the outer layers of the brain (cerebral cortex) and in specialized neurons in the brain and spinal cord that control movement (motor neurons). The *C9orf72* protein is thought to be located at the tip of the neuron in a region called the presynaptic terminal. This area is important for sending and receiving signals between neurons.

The *C9orf72* protein likely plays a role in many processes involving the chemical cousin of DNA, known as RNA. This protein is thought to influence the production of RNA from genes, the production of proteins from RNA, and the transport of RNA within the cell.

The *C9orf72* gene contains a segment of DNA made up of a series of six DNA building blocks (nucleotides), four guanines followed by two cytosines (written as GGGGCC). This segment (known as a hexanucleotide repeat) can occur once or be repeated multiple times in a row; estimates suggest repeats of up to 30 times have no negative effect on gene function.

Health Conditions Related to Genetic Changes

amyotrophic lateral sclerosis

Mutations in the *C9orf72* gene have been found to cause amyotrophic lateral sclerosis (ALS), a condition characterized by progressive muscle weakness, a loss of muscle mass, and an inability to control movement. These mutations affect the GGGGCC segment of the gene. When this series of nucleotides is repeated too many times, it can cause ALS. This type of mutation is called a hexanucleotide repeat expansion. Although it is not clear exactly how many hexanucleotide repeats are needed to cause disease, researchers believe that having more than about 30 repeats can lead to ALS.

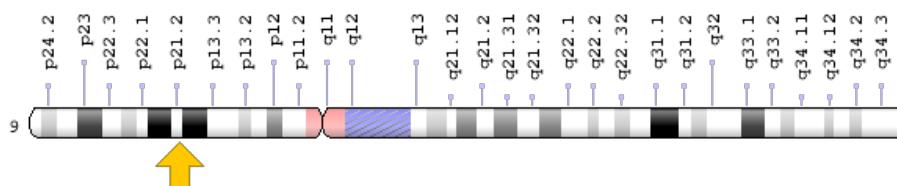
It is unclear whether the hexanucleotide repeat expansion reduces *C9orf72* protein function or leads to the production of a protein with abnormal function that disrupts RNA and protein production in the cell, resulting in the formation of protein clumps (aggregates). In ALS, the large size of motor neurons is thought to make these cells vulnerable to impairments in normal cell function. Disruptions in *C9orf72* protein function may lead to premature motor neuron cell death, resulting in the signs and symptoms of ALS.

Some people with ALS caused by *C9orf72* gene mutations also develop a condition called frontotemporal dementia (FTD), which is a progressive brain disorder that affects personality, behavior, and language. It is unclear why some people with *C9orf72* gene mutations develop FTD and others do not. Individuals who develop both conditions are diagnosed as having ALS-FTD.

Chromosomal Location

Cytogenetic Location: 9p21.2, which is the short (p) arm of chromosome 9 at position 21.2

Molecular Location: base pairs 27,546,546 to 27,573,866 on chromosome 9 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- CI072_HUMAN
- MGC23980
- uncharacterized protein C9orf72

Additional Information & Resources

Educational Resources

- Washington University, St. Louis Neuromuscular Disease Center: C9orf72-associated ALS-FTD
<http://neuromuscular.wustl.edu/synmot.html#alsftd2>

GeneReviews

- Amyotrophic Lateral Sclerosis Overview
<https://www.ncbi.nlm.nih.gov/books/NBK1450>
- C9orf72-Related Amyotrophic Lateral Sclerosis and Frontotemporal Dementia
<https://www.ncbi.nlm.nih.gov/books/NBK268647>

Scientific Articles on PubMed

- PubMed

<https://www.ncbi.nlm.nih.gov/pubmed?term=%28C9orf72%5BTI%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+360+days%22%5Bdp%5D>

OMIM

- CHROMOSOME 9 OPEN READING FRAME 72
<http://omim.org/entry/614260>

Research Resources

- ClinVar
<https://www.ncbi.nlm.nih.gov/clinvar?term=C9orf72%5Bgene%5D>
- HGNC Gene Family: DENN/MADD domain containing
<http://www.genenames.org/cgi-bin/genefamilies/set/504>
- HGNC Gene Symbol Report
http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=28337
- NCBI Gene
<https://www.ncbi.nlm.nih.gov/gene/203228>
- UniProt
<http://www.uniprot.org/uniprot/Q96LT7>

Sources for This Summary

- OMIM: CHROMOSOME 9 OPEN READING FRAME 72
<http://omim.org/entry/614260>
- Chiò A, Borghero G, Restagno G, Mora G, Drepper C, Traynor BJ, Sendtner M, Brunetti M, Ossola I, Calvo A, Pugliatti M, Sotgiu MA, Murru MR, Marrosu MG, Marrosu F, Marinou K, Mandrioli J, Sola P, Caponnetto C, Mancardi G, Mandich P, La Bella V, Spataro R, Conte A, Monsurrò MR, Tedeschi G, Pisano F, Bartolomei I, Salvi F, Lauria Pinter G, Simone I, Logroscino G, Gambardella A, Quattrone A, Lunetta C, Volanti P, Zollino M, Penco S, Battistini S; ITALSGEN consortium, Renton AE, Majounie E, Abramzon Y, Conforti FL, Giannini F, Corbo M, Sabatelli M. Clinical characteristics of patients with familial amyotrophic lateral sclerosis carrying the pathogenic GGGGCC hexanucleotide repeat expansion of C9ORF72. *Brain.* 2012 Mar;135(Pt 3):784-93. doi: 10.1093/brain/awr366.

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- DeJesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker M, Rutherford NJ, Nicholson AM, Finch NA, Flynn H, Adamson J, Kouri N, Wojtas A, Sengdy P, Hsiung GY, Karydas A, Seeley WW, Josephs KA, Coppola G, Geschwind DH, Wszolek ZK, Feldman H, Knopman DS, Petersen RC, Miller BL, Dickson DW, Boylan KB, Graff-Radford NR, Rademakers R. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. *Neuron*. 2011 Oct 20;72(2):245-56. doi: 10.1016/j.neuron.2011.09.011. Epub 2011 Sep 21. *Citation on PubMed*: <https://www.ncbi.nlm.nih.gov/pubmed/21944778> *Free article on PubMed Central*: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3202986/>
- Farg MA, Sundaramoorthy V, Sultana JM, Yang S, Atkinson RA, Levina V, Halloran MA, Gleeson PA, Blair IP, Soo KY, King AE, Atkin JD. C9ORF72, implicated in amyotrophic lateral sclerosis and frontotemporal dementia, regulates endosomal trafficking. *Hum Mol Genet*. 2014 Jul 1;23(13):3579-95. doi: 10.1093/hmg/ddu068. Epub 2014 Feb 18. *Citation on PubMed*: <https://www.ncbi.nlm.nih.gov/pubmed/24549040> *Free article on PubMed Central*: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4049310/>
- Majounie E, Renton AE, Mok K, Dopper EG, Waite A, Rollinson S, Chiò A, Restagno G, Nicolaou N, Simon-Sánchez J, van Swieten JC, Abramzon Y, Johnson JO, Sendtner M, Pamphlett R, Orrell RW, Mead S, Sidle KC, Houlden H, Rohrer JD, Morrison KE, Pall H, Talbot K, Ansorge O; Chromosome 9-ALS/FTD Consortium; French research network on FTLD/FTLD/ALS; ITALSGEN Consortium, Hernandez DG, Arepalli S, Sabatelli M, Mora G, Corbo M, Giannini F, Calvo A, Englund E, Borghero G, Floris GL, Remes AM, Laaksovirta H, McCluskey L, Trojanowski JQ, Van Deerlin VM, Schellenberg GD, Nalls MA, Drory VE, Lu CS, Yeh TH, Ishiura H, Takahashi Y, Tsuji S, Le Ber I, Brice A, Drepper C, Williams N, Kirby J, Shaw P, Hardy J, Tienari PJ, Heutink P, Morris HR, Pickering-Brown S, Traynor BJ. Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. *Lancet Neurol*. 2012 Apr;11(4):323-30. doi: 10.1016/S1474-4422(12)70043-1. Epub 2012 Mar 9. *Citation on PubMed*: <https://www.ncbi.nlm.nih.gov/pubmed/22406228> *Free article on PubMed Central*: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3322422/>
- Smith BN, Newhouse S, Shatunov A, Vance C, Topp S, Johnson L, Miller J, Lee Y, Troakes C, Scott KM, Jones A, Gray I, Wright J, Hortobágyi T, Al-Sarraj S, Rogelj B, Powell J, Lupton M, Lovestone S, Sapp PC, Weber M, Nestor PJ, Schelhaas HJ, Asbroek AA, Silani V, Gellera C, Taroni F, Ticozzi N, Van den Berg L, Veldink J, Van Damme P, Robberecht W, Shaw PJ, Kirby J, Pall H, Morrison KE, Morris A, de Belleroche J, Vianney de Jong JM, Baas F, Andersen PM, Landers J, Brown RH Jr, Weale ME, Al-Chalabi A, Shaw CE. The C9ORF72 expansion mutation is a common cause of ALS+/-FTD in Europe and has a single founder. *Eur J Hum Genet*. 2013 Jan; 21(1):102-8. doi: 10.1038/ejhg.2012.98. Epub 2012 Jun 13. *Citation on PubMed*: <https://www.ncbi.nlm.nih.gov/pubmed/22692064> *Free article on PubMed Central*: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3522204/>
- Zhang K, Donnelly CJ, Haeusler AR, Grima JC, Machamer JB, Steinwald P, Daley EL, Miller SJ, Cunningham KM, Vidensky S, Gupta S, Thomas MA, Hong I, Chiu SL, Huganir RL, Ostrow LW, Matunis MJ, Wang J, Sattler R, Lloyd TE, Rothstein JD. The C9orf72 repeat expansion disrupts nucleocytoplasmic transport. *Nature*. 2015 Sep 3;525(7567):56-61. doi: 10.1038/nature14973. Epub 2015 Aug 26. *Citation on PubMed*: <https://www.ncbi.nlm.nih.gov/pubmed/26308891> *Free article on PubMed Central*: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4800742/>

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